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CARPROFEN IN VETERINARY MEDICINE II. INHIBITORY EFFECT ON THE RELEASE OF $PGF_{2\alpha}$ IN THE EARLY POSTPARTUM COW

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SUMMARY

Carprofen, a non-steroidal anti-inflammatory drug (NSAID) known to inhibit prostaglandin synthesis, was given intravenously in five cows at a daily dose of 0.7 mg/kg for five days beginning on day 1 postpartum. Blood samples were collected at various times over a period of six days following the first injection. At this dose, carprofen reached highest plasma values of about 45 μg/ml after the fifth injection and was well tolerated by all the cows. During the whole experimental period, mean plasma levels of 15-keto-13, 14-dihydro-prostaglandin $F_{2\alpha}$, the primary metabolite of $PGF_{2\alpha}$, were significantly ($p<0.05$) lower in treated than in control animals (28–47% vs 64–101% of pretreatment concentrations). The suppressive effect of carprofen on $PGF_{2\alpha}$-production occurred immediately after its application and was maximal 3–6 h post injectionem on the first and on the fifth experimental day (60–80% and 40–85%, respectively).

We conclude from our results that carprofen in a single dose of 0.7 mg/kg b. w. effectively suppresses $PGF_{2\alpha}$-release in the postpartum cow. Whether this effect is beneficial in the treatment of uterine inflammatory processes remains to be determined.

KEY WORDS: non-steroidal anti-inflammatory drug – carprofen – prostaglandin $F_{2\alpha}$ – puerperium – cow

CARPROFEN IN DER VETERINÄRMEDIZIN. II. HEMMUNG DER FREISETZUNG VON $PGF_{2\alpha}$ BEI FRISCH GEKALBTEN KÜHEN

Carprofen, ein nichtsteroidales, entzündungshemmendes Medikament (NSAID), mit der Eigenschaft, die Prostaglandin-Synthese bei gewissen Tierarten zu hemmen, wurde fünf Kühen in einer täglichen Dosierung von 0,7 mg/kg KGW vom ersten Tag postpartum an während fünf Tagen intravenös verabreicht. Während sechs Tagen nach der ersten Injektion wurden in verschiedenen Zeitabständen Blutproben entnommen. In obiger Dosierung wurde Carprofen, dessen Konzentration im Blutplasma nach der fünften Injektion bis auf 45 μg/ml anstieg, von allen Kühen gut vertragen. Während der gesamten Versuchsdauer waren die mittleren Plasmakonzentrationen von 15-keto-13, 14-dihydro-Prostaglandin $F_{2\alpha}$, dem Hauptmetaboliten von $PGF_{2\alpha}$, bei den behandelten Tieren signifikant ($p<0,05$) tiefer als bei den Kontrolltieren (28–47% vs 64–101%, bezogen auf die Anfangskonzentrationen). Die suppressive Wirkung von Carprofen auf die $PGF_{2\alpha}$-Produktion setzte unmittelbar nach dessen Verabreichung ein und war sowohl am ersten wie auch am fünften Versuchstag 3–6 Stunden post injectionem am grössten (60–80% bzw. 40–85%).

Unsere Ergebnisse zeigen, dass Carprofen in einmaliger Dosierung von 0,7 mg/kg KGW die postpartale $PGF_{2\alpha}$-Sekretion bei Kühen wirkungsvoll zu unterdrücken vermag. Ob diese Wirkung bei der Behandlung der Gebärmutterentzündung der Kühe ausgenutzt werden kann, sollte in weiteren Untersuchungen abgeklärt werden.

SCHLÜSSELWÖRTER: nichtsteroidales antiinflammatorisches Medikament – Carprofen – Prostaglandin $F_{2\alpha}$ – Puerperium – Kuh

The early postpartum uterus of the cow releases large amounts of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) that usually return to baseline levels about 15 days after parturition (*Edqvist* et al., 1978; *Guilbault* et al., 1984; *Madej* et al., 1984). In cows with a normal puerperium a significant negative correlation has been demonstrated between the duration of ele-

vated peripheral concentrations of the metabolite 15-keto-13, 14-dihydro-prostaglandin $F_{2\alpha}$ (PGFM) postpartum and the time required for completion of uterine involution (*Eley* et al., 1981; *Lindell* et al., 1982; *Kindahl* et al., 1984). Furthermore, massive doses of exogenous $PGF_{2\alpha}$ or its analogues have been shown to hasten the involution of the uterus (*Lindell* and *Kindahl*, 1983) and to shorten the interval from parturition to onset of ovarian activity (*Etherington*, 1984).

These findings alone, however, do not explain the role of $PGF_{2\alpha}$ in uterine involution, especially in light of recent reports that the postpartum uterus in the cow is relatively insensitive to exogenously administered $PGF_{2\alpha}$ (*Eiler* et al., 1984; *Ko* et al., 1985) and that neither partial suppression of $PGF_{2\alpha}$ synthesis (*Gustafsson* et al., 1986; *Guilbault* et al., 1987) nor continuous infusion of $PGF_{2\alpha}$ early in the puerperium (*Guilbault* et al., 1988) were found to influence the rate of uterine involution. Therefore, experiments were designed to specifically investigate the physiological meaning of high postpartum $PGF_{2\alpha}$ levels on the process of uterine involution. The aim of the present study was to determine the potency of carprofen[1] [(±)-6-chloro-2-methylcarbazole-2-acetic acid], a prostaglandin cyclooxygenase inhibitor, for suppression of endogenous uterine $PGF_{2\alpha}$ production in the early postpartum cow.

MATERIALS AND METHODS

Animals and blood collection

Five pregnant cows of Schweizer Braunvieh breed, between 5 and 11 years old, weighing 530–695 kg, were used for the study. The animals were kept in individual indoor pens and were fed twice daily with hay and a commercial standard diet and water ad libitum. Carprofen (5%-solution) was injected into the right jugular vein at a dose rate of 0.7 mg/kg b. w. daily for five days beginning on day 1 after calving. The injected volume ranged from 6.3 to 10.2 ml, and the injection lasted for 20–30 seconds. Four cows receiving 10 ml of 0.9% (w/v) NaCl solution only served as controls.

Blood samples (20 ml) were collected from the left jugular vein into heparinized glass tubes (Vacutainer®, Becton Dickson, France SA) before and at various times over a period of six days following the first injection of carprofen. The blood was immediately centrifuged and the plasma was harvested and stored at -20°C in glass tubes until analysis.

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Assay procedures

Plasma samples were assayed for carprofen in duplicate on two different days by means of an HPLC method using a normal phase technique as described by *Ludwig* et al., (1989). The drug and the internal standard Ro 21-0134 (rac. 2-(6-chloro-2-carbazolyl)-propanol) were extracted from the plasma buffered to pH 2.8 using butyl acetate. The plasma extracts were injected directly and the eluent from the analytical column was monitored by a fluorometric detector (Fluorescence Detector HP 1046A) operated at 245 nm for excitation and 375 nm for emission. The limit of quantitative determination of carprofen was 0.04 μg/ml in plasma, with an accuracy and precision better than 10% when using 1-ml plasma volume.

The main plasma metabolite of $PGF_{2\alpha}$, $F_{2\alpha}$, 15-keto-13, 14-dihydro-prostaglandin $F_{2\alpha}$ (PGFM), was analysed by radioimmunoassay according to *Granström* and *Kindahl* (1982). The detection limit of the assay is 30 pmol/l.

Statistical analysis

Comparison of means of percent PGFM inhibition between the control (saline) and treatment (carprofen) group over the whole period of time was made by 2-factor repeated measures analysis of variance. Differences in mean PGFM inhibition, calculated as percent of pretreatment concentrations, between the two groups at various time intervals after the first injection were tested, using a 1-tailed Student's t-test. Statistical significance was assessed at the 5% level.

Results

Peripheral concentrations of PGFM during the first 6 days (144 h) of the experiment are shown in figure 1. On day 1 postpartum, before beginning treatment, plasma PGFM levels ranged between 2.4–12.6 and 2.9–4.4 nmol/l, in the treated and control groups, respectively. As expected in control animals given only saline, elevated peripheral PGFM values of more than 4 nmol/l on day 1 postpartum progressively decreased to values between 1.5 and 3 nmol/l plasma, 6 days (144 h) later. In cows given carprofen at 0.7 mg/kg b. w., however, pretreatment PGFM concentrations as high as 12 nmol/l rapidly declined to levels below 2.5 nmol/l plasma within 24 hours following the first of the series of 5 daily injections. Although PGFM levels in the peripheral circulation remained clearly suppressed in treated animals (1.0–1.8 nmol/l) compared to the control group (2.1–3.5 nmol/l) throughout the experiment, a transient

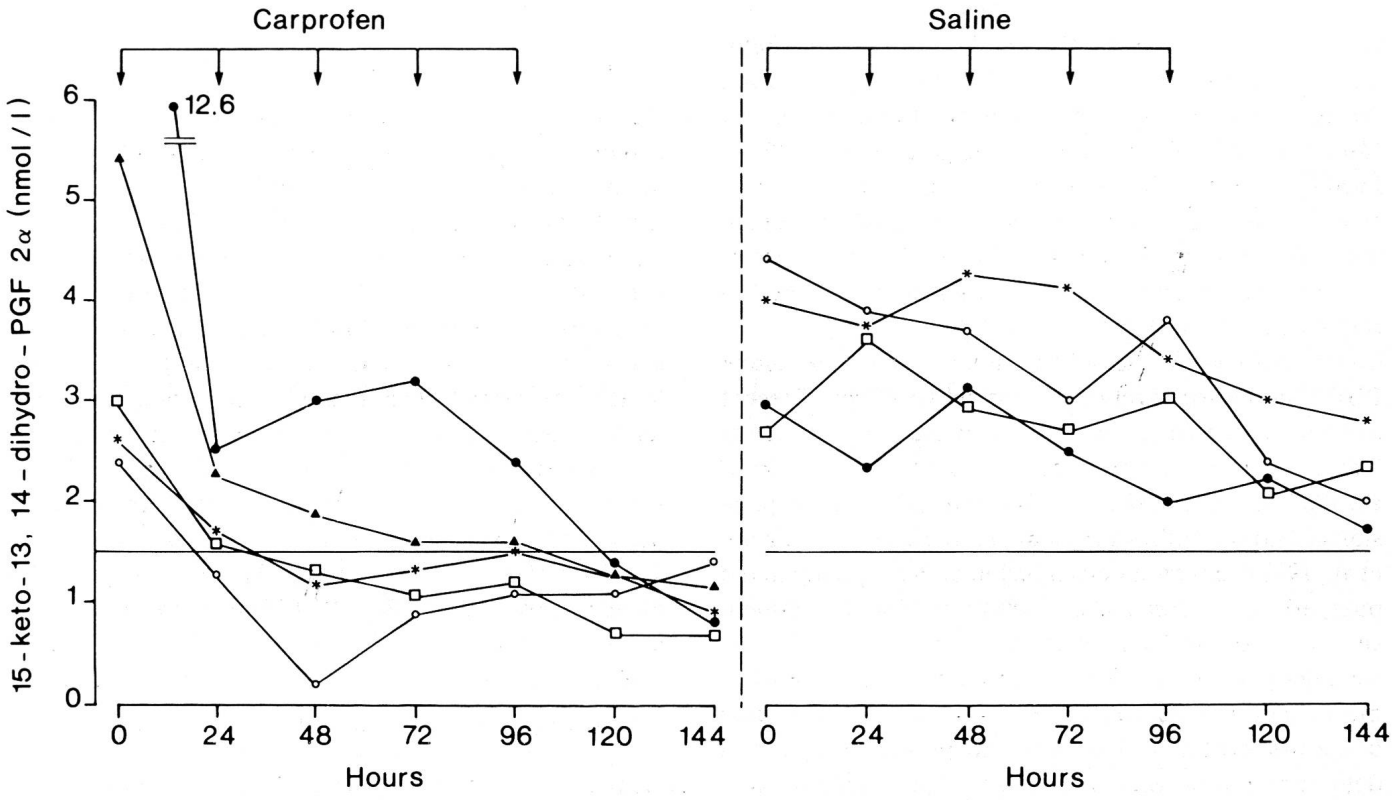

Fig. 1: Plasma concentrations of 15-keto-13, 14-dihydro-$PGF_{2\alpha}$ in cows treated from days 1 to 5 postpartum with carprofen or physiological saline. Arrows indicate time of injection.

rise of PGFM from 2.5 to 3.2 nmol/l plasma was observed in one cow between 24 and 72 hours after beginning drug administration. One day after the last carprofen injection (120 h), PGFM values were less than 1.5 nmol/l plasma. Inhibition of PGFM production, as expressed as the percentage of pretreatment concentrations on day 1 postpartum, was significantly ($p < 0.05$) greater for cows given carprofen compared with saline, for all time intervals examined (figure 2; table).

Efficiency of carprofen in inhibiting synthesis of $PGF_{2\alpha}$ was evaluated in 5 cows by measuring PGFM and carprofen concentrations concomitantly at various time intervals (0.25, 0.5, 0.75, 2, 3, 5, 6, 10 hours) following the first (figure 3) and fifth injection (figure 4) of the prostaglandin cyclooxygenase inhibitor. Highest carprofen levels between 7.8–15.8 µg/ml on day 1 and 22.8–43.7 µg/ml on day 5 were observed 15 minutes after the intravenous injection and gradually decreased to mean values of 6.7 and 18.3 µg/ml 10 hours later on these two test days. During the same period of time, pre-injection peripheral PGFM concentrations ranging between 2.4–12.6 nmol/l on day 1 and 1.1–2.4 nmol/l on day 5, declined rapidly to minima within 3 to 6 hours post injectionem, with values between 0.9–3.5 and 0.4–1.4 nmol/l plasma, respectively. From 6 to 10 hours after the carprofen injections on day 1 and 5 a clear tendency for PGFM levels to increase was observed in all cows. The suppressive effect of carprofen during the first 3 hours after the intravenous administration calculated as percent of the pre-injection values on the first und fifth experimental day ranged from about 60–80% and 40–85%, respectively.

DISCUSSION

Carprofen is a newly developed non-steroidal anti-inflammatory drug (NSAID) like acetylsalicylic acid, phenylbutazone, indomethacin or flunixin meglumine. These drugs reduce the cardinal signs of inflammation including vasodilatation, edema and pain. The mechanism by which the NSAIDs alleviate many of the metabolic, hemodynamic and clinical changes of inflammation is thought to be through inhibition of the cyclooxygenase enzyme, thereby reducing the formation of biologically active prostaglandins from arachidonic acid *(Lewis,* 1983). These findings

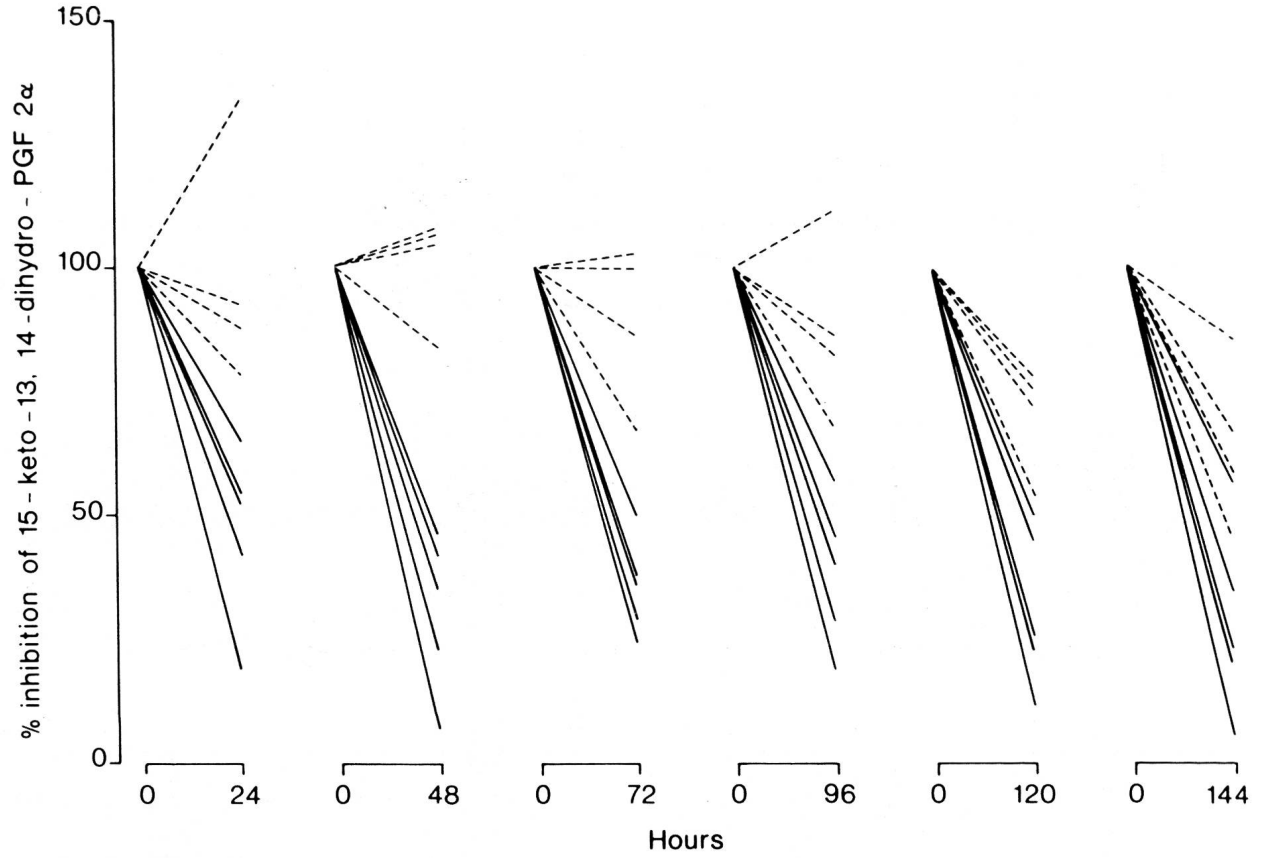

Fig. 2: Percent inhibition of pretreatment plasma concentrations of 15-keto-13, 14-dihydro-$PGF_{2\alpha}$ at various time intervals in cows treated with carprofen (solid lines) or physiological saline (dottet lines).

Table: Mean (SD, SE) concentrations of 15-keto-13, 14-dihydro-$PGF_{2\alpha}$ in control and carprofen treated cows at various time intervals.

Time[c] (h)		0	24	48	72	96	120	144
Control	$\bar{x}$[a]	3.50	3.38	3.48	3.08	3.03	2.40	2.18
(n = 4)	SD	0.83	0.73	0.59	0.71	0.76	0.36	0.43
Carprofen	$\bar{x}$[a]	5.20	1.88	1.52	1.62	1.56	1.16	1.00
(n = 5)	SD	4.31	0.50	1.03	0.92	0.51	0.28	0.29
Control[d]	$\bar{x}_1^b$	100	98.43	100.80	89.20	87.20	70.13	64.15
	SD	–	23.90	11.25	15.79	17.60	10.64	16.66
Carprofen[d]	$\bar{x}_2^b$	100	47.00	31.32	35.80	38.40	30.84	28.94
	SD	–	17.21	15.51	9.41	14.83	16.46	19.26
$\bar{x}_1 - \bar{x}_2$	$\bar{d}$	0	51.43[e]	69.48[e]	53.40[e]	48.80[e]	39.29[e]	35.21[e]
	SE	–	13.65	9.29	8.42	10.78	9.57	8.61

[a] all values in nmol/l

[b] all values in percent of pretreatment concentrations

[c, d] significant effects between time and groups ($p < 0.05$)

[e] significant differences between groups at each time interval ($p < 0.05$)

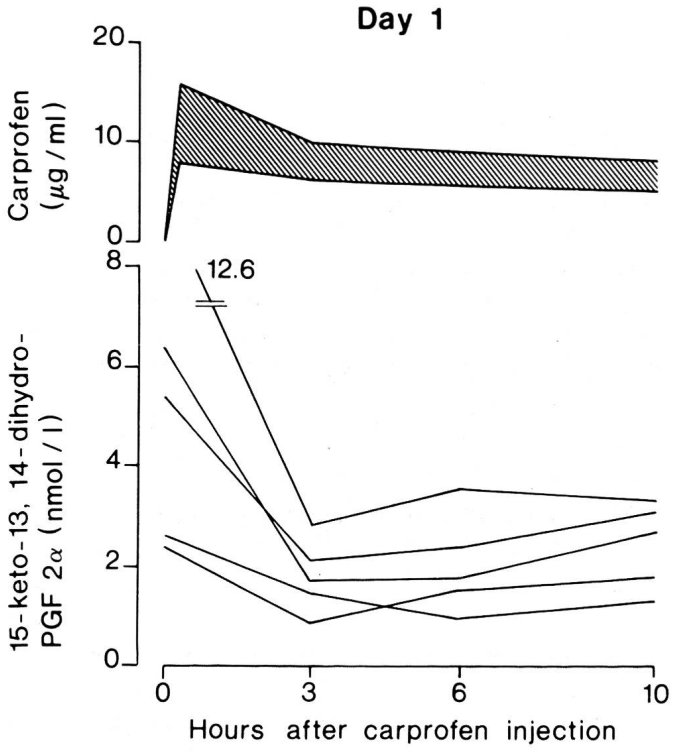

Fig. 3: Plasma concentrations of carprofen (min-max) and 15-keto-13, 14-dihydro-$PGF_{2\alpha}$ in 5 cows during 10 hours after the first carprofen injection (day 1 postpartum).

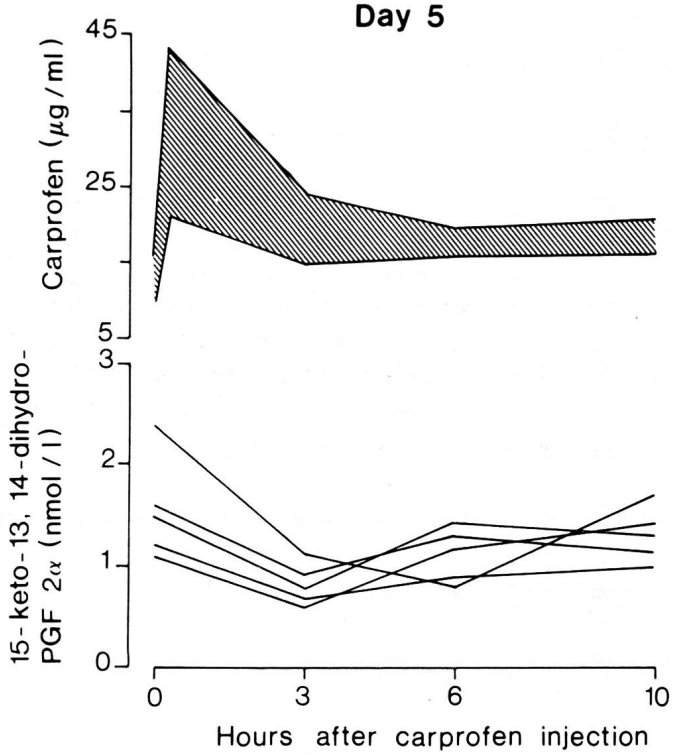

Fig. 4: Plasma concentrations of carprofen (min-max) and 15-keto-13, 14-dihydro-$PGF_{2\alpha}$ in 5 cows during 10 hours after the fifth carprofen injection (day 5 postpartum).

indicate that prostaglandins and other arachidonic acid metabolites such as leukotrienes formed by the action of lipoxygenase are involved in the development of inflammatory processes.

Inflammation is characterized by various forms of injury (physical, chemical, thermal, bacterial, viral) causing the local release of chemical mediators such as histamine, serotonin (5-HT), kinins, complement, interleukin-1 and eicosanoids (prostaglandins and leukotrienes). All these mediators produce edema, pain and attract leukocytes (macrophages) to the injured area. Although the individual contribution of each of these mediators is difficult to assess, the eicosanoids (especially prostaglandin E_2, prostaglandin I_2, thromboxane A_2, leukotriene B_4) are regarded as crucial in the inflammatory response in that they may modulate or amplify the effects of other mediators (*Dahlen* et al., 1981) and sustain inflammation.

Therefore, one of the current therapeutical approaches to reduce pain and pyrexia caused by the inflammatory process is the administration of drugs which inhibit the cyclooxygenase enzyme system. Dual inhibitors (cyclooxygenases and lipoxygenases) have also been successfully synthesized but clinical results were disappointing, mainly because of their high dosage rates, poor penetration into inflammatory exudate and limited antiprostaglandin activity (*Lees* et al., 1987).

Although NSAIDs are known to act by the same mechanism (inhibition of cyclooxygenase), their use in clinical cases suggests marked differences in their analgesic, antipyretic and antiphlogistic activity, depending on the species, the tissue type and even the cause of the inflammation. For example, phenylbutazone is recognized as being excellent in the horse for the relief of pain associated with the locomotor system, but is less effective than flunixin for the treatment of colic (*May* et al., 1987). Also the pharmacokinetic properties and the toxicity of these compounds relative to their effective dose vary considerably. In cattle, phenylbutazone has a plasma half-life of between 32 and 78 h contrasting with 3.5–4 h in the horse (*Eberhardson* et al., 1979). The toxicity of phenylbutazone, however, may limit its use in cattle as *Martin* et al. (1984) have reported a considerable decrease in the total number of leukocytes af-

ter 5-days treatment with 5 mg/kg twice daily. On the other hand flunixin meglumine in cattle has a plasma half-life of only about 8 h *(Hardee* et al., 1985) compared to 44–65 h for carprofen after repeated daily injections *(Ludwig* et al., 1989).

Our present study clearly demonstrates that carprofen given intravenously at a daily dose of 0.7 mg/kg b.w. for 5 days effectively suppressed $PGF_{2\alpha}$ release, measured as plasma PGFM concentrations, in the early postpartum cow. Moreover, at this dose rate carprofen was well tolerated by all cows, the important blood parameters remaining within the normal range during the whole treatment period *(Ludwig* et al., 1989). A similar $PGF_{2\alpha}$ suppressive effect has also been shown for flunixin *(Gustafsson* et al., 1986; *Guilbault* et al., 1987) when given i.m. at the recommended dose of 2.2 mg/kg b.w. twice daily. In addition, when following the peripheral PGFM concentrations after a single injection of either flunixin or carprofen, maximal inhibition as high as 80% occurred between 3 and 6 h with both drugs. The lower dosage (only one third of that of flunixin), however, and the longer administration interval (only once a day) make carprofen an attractive drug for econimical as well as practical reasons. Considering its maximal effect, which will last 6 h at the most, the following alternatives should be taken into account for future experiments: a) to increase the maintenance dose with or without a higher initial loading dose, b) to increase the frequency of administration or c) a combination of both.

The precise role of high $PGF_{2\alpha}$ production early in the puerperium is uncertain. Cows with retained placentas or persistent uterine infections postpartum have a prolonged release of $PGF_{2\alpha}$ *(Kindahl* et al., 1984; *Fredriksson* et al., 1985) due either to repair processes in the uterus *(Kindahl* et al., 1977) or to bacterial endotoxins which have been shown to stimulate $PGF_{2\alpha}$ release in several species *(Kindahl* et al., 1986).

These considerations prompted the present investigation. As flunixin has been shown to be beneficial in controlling inflammatory reactions in horses *(May* et al., 1987), calves *(Selman* et al., 1984) and cows *(Anderson* et al., 1986), further research is planned with carprofen with the objective of developing a more effective anti-inflammatory agent for therapeutic use in bovine endometrial disease and/or mastitis. Finally the removal of pain by potent NSAIDs which has always been ethically desirable and has become part of the veterinarian's oath may return the animals to productivity by preventing anorexia and recumbency.

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Carprofen en médecine vétérinaire II. Effet inhibiteur sur la synthèse de la prostaglandine $F_{2\alpha}$ chez la vache postpartale

Le Carprofen, un anti-inflammatoire non-stéroïdien (AINS), inhibe la synthèse de la prostaglandine $F_{2\alpha}$, des médiateurs de l'inflammation, chez les animaux de laboratoire. Afin de vérifier cet effet chez les bovins, une dose journalière de 0.7 mg de Carprofen/kg de poids vif a été injectée par voie intraveineuse à cinq vaches, dès le premier jour après la mise-bas, et pendant les quatre jours qui ont suivi. Le Carprofen, ainsi que le principal métabolite de la prostaglandine $F_{2\alpha}$ ($PGF_{2\alpha}$), la 15-céto-13,14-dihydro-prostaglandine $F_{2\alpha}$, ont été dosés dans les plasmas obtenus à partir d'échantillons de sang prélevés pendant les six jours suivant la première injection.

Dans cette expérience, il a été démontré que le Carprofen était particulièrement bien toléré par les cinq vaches. Sa concentration plasmatique maximale a atteint 45 μg/ml. Par ailleurs, chez les vaches ayant reçu le Carprofen, les concentrations plasmatiques de la $PGF_{2\alpha}$ étaient plus faibles que celles mesurées chez les vaches non traitées, cette différence était statistiquement significative ($p < 0.05$). Ainsi, la concentration plasmatique moyenne du principal metabolite de la $PGF_{2\alpha}$ des cinq vaches traitées avec le Carprofen, est restée de 64 à 101% inférieure à la concentration mesurée juste avant la première injection, et cela pendant toute la durée du traitement. Il peut donc être conclu que le Carprofen exerce, *in vivo*, un effet inhibiteur sur la biosynthèse de la prostaglandine $PGF_{2\alpha}$ chez la vache. L'inhibition maximale se produit pendant les 3 à 6 premières heures suivant l'injection intraveneuse. La posologie de 0.7 mg/kg par jour est suffisante pour inhiber la biosynthèse des prostaglandines durant les 24 heures qui suivent l'injection du Carprofen.

Dans des essais cliniques à venir, l'efficacité thérapeutique du Carprofen va être testée chez la vache présentant des complications inflammatoires après avoir vêllé.

Carprofen nella medicina veterinaria II. Effetto inibitore sullo secrezione di $PGF_{2\alpha}$ nello vacca successivamente al parto

Carprofen, un medicamento antiflogistico non appartenente agli steroidi (NSAID), avente la proprietà di arrestare la sintesi delle prostaglandine in alcuni animali, è stato somministrato giornalmente a 5 vacche a partire dal primo giorno dopo il parto, per via endovenosa, nella concentrazione di 0.7 mg/kg di peso corporeo.

Durante i 6 giorni successivi alla prima iniezione sono state prelevate prove sanguinee in differenti intervalli di tempo. Nella dose sopra indicata il Carprofen, la cui concentrazione plasmatica dopo la quinta iniezione è salita fino a 45 μg/ml, è stato sopportato da tutti gli animali.

Nel corso dell'esperimento le concentrazioni plasmatiche del 15-keto-13, 14-dihydro-$PGF_{2\alpha}$, il prodotto metabolico

principale della $PGF_{2\alpha}$, si è dimostrato significativamente più basso ($p < 0.05$) rispetto ai valori degli animali di controllo (28–47% confrontati ai 64–101% per quanto concerne le concentrazioni iniziali).
L'effetto sopressivo del Carprofen sulla produzione della $PGF_{2\alpha}$ è cominciato subito dopo la somministrazione e raggiungeva al primo come all'ultimo giorno dell'esperimento, l'intensità massima da 3 a 6 ore dopo l'iniezione (60–80% rispettivamente 40–85%).
I nostri risultati dimostrano come il Carprofen, nella dose unica di 0.7 mg/kg di peso corporeo, possa effettivamente sopprimere la secrezione della $PGF_{2\alpha}$ nelle vacche postpartale. L'utilizzazione di questo effetto nella terapia delle infiammazioni dell'utero nel bovino, dev'essere ancora dimostrata tramite ulteriori analisi.

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